# U.S. PATENT APPLICATION

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*Invention:*    OPTICALLY ACTIVE FLUORINE-CONTAINING COMPOUNDS AND
          PROCESSES FOR THEIR PRODUCTION

# *SPECIFICATION*

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## OPTICALLY ACTIVE FLUORINE-CONTAINING COMPOUNDS AND PROCESSES FOR THEIR PRODUCTION

The present invention relates to optically active
fluorine-containing novel compounds, processes for their
5    production, and processes for producing optically active
3,3,3-trifluoro-2-hydroxy-2-methylpropionic acids,
employing them.

The optically active fluorine-containing compounds
of the present invention are compounds useful as
10   intermediates for pharmaceuticals or agricultural
chemicals. For example, an optically active benzyl ester
of 2,3-epoxy-$\alpha$,$\alpha$,$\alpha$,-trifluoropropionic acid as one of
such compounds, can readily be led to optically active
3,3,3-trifluoro-2-hydroxy-2-methylpropionic acid which is
15   known as a compound very useful as an intermediate for
pharmaceuticals or agricultural chemical.

As a process for producing optically active 3,3,3-
trifluoro-2-hydroxy-2-methylpropionic acid, a production
method by optical resolution of racemic 3,3,3-trifluoro-
20   2-hydroxy-2-methylpropionic acid by means of e.g.

optically active α-phenylethylamine, has, for example, been known (e.g. JP-A-5-286915, J. Chem. Soc., 2329-2332, 1951, or J. Med. Chem., 39, 4592-4601, 1996).

Further, a process is known wherein racemic 3,3,3-trifluoro-2-hydroxy-2-methylpropionic acid ester derivative is hydrolyzed by means of lipase to produce optically active 3,3,3-trifluoro-2-hydroxy-2-methylpropionic acid (e.g. WO97/38124).

However, the production process employing an optical resolution agent, has a problem in the efficiency, since it is necessary to repeat recrystallization at least few times, and it is required to carry out a treatment to remove the optical resolution agent.

Further, in the process employing lipase, it is not possible to racemize the unnecessary optical antipode and to reuse it as a starting material, at the time of producing 3,3,3-trifluoro-2-hydroxy-2-methylpropionic acid. Thus, such a process can not be regarded as an advantageous process.

Further, no process has been known in which optically active 3,3,3-trifluoro-2-hydroxy-2-methylpropionic acid is produced efficiently by an asymmetric synthesis.

The present inventors have conducted an extensive study on a process for producing optically active 3,3,3-trifluoro-2-hydroxy-2-methylpropionic acid to solve the above-mentioned problems and as a result, have found that

an optically active benzyl ester of 2,3-epoxy-α,α,α,-
trifluoropropionic acid can be led to a novel optically
active 2,3-epoxy-α,α,α,-trifluoropropionic acid by a
hydrogenation reaction, and further that by reacting such

5   a compound with a metal hydride, optically active 3,3,3-
trifluoro-2-hydroxy-2-methylpropionic acid can be
produced easily and efficiently. Further, they have been
found that novel optically active fluorine-containing
compounds including the optically active benzyl ester of

10  2,3-epoxy-α,α,α,-trifluoropropionic acid, can be obtained
by asymmetrically epoxidizing specific α,α,α,-
trifluoromethacrylic acid derivatives. The present
invention has been accomplished on the basis of these
discoveries.

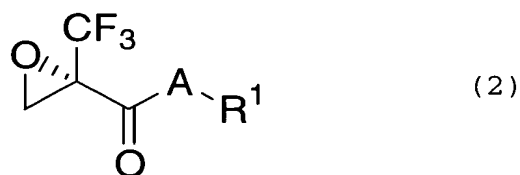15      Namely, the present invention provides:

        1.  An optically active fluorine-containing compound
represented by the following formula (1):
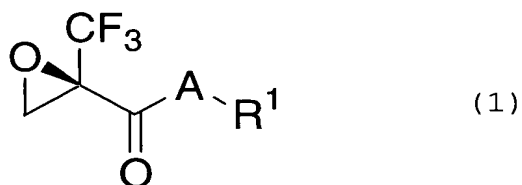


wherein A is an oxygen atom, a sulfur atom or an NH group,
20  and $R^1$ is a methyl group, an ethyl group, a $C_{3-10}$ linear,
branched or cyclic alkyl group, a $C_{6-20}$ aromatic group, a
$C_{6-20}$ aromatic group having hydrogen on the aromatic ring
optionally substituted by a halogen atom, a $C_{6-20}$ aromatic
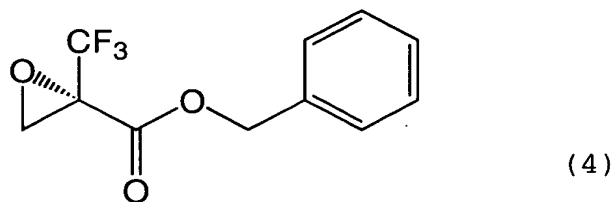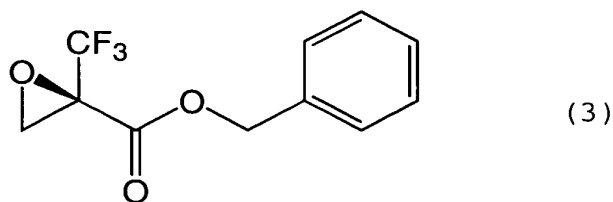group having hydrogen on the aromatic ring optionally

substituted by a methyl group, a $C_{6-20}$ aromatic group having hydrogen on the aromatic ring optionally substituted by an ethyl group, a $C_{6-20}$ aromatic group having hydrogen on the aromatic ring optionally

5    substituted by a $C_{3-6}$ linear, branched or cyclic alkyl group, a $C_{6-20}$ aromatic group having hydrogen on the aromatic ring optionally substituted by a methoxy group, a $C_{6-20}$ aromatic group having hydrogen on the aromatic ring optionally substituted by an ethoxy group, a $C_{6-20}$

10   aromatic group having hydrogen on the aromatic ring optionally substituted by a $C_{3-6}$ linear, branched or cyclic alkyloxy group, a $C_{5-19}$ heteroaromatic group, a $C_{5-19}$ heteroaromatic group having hydrogen on the aromatic ring optionally substituted by a halogen atom, a $C_{5-19}$

15   heteroaromatic group having hydrogen on the aromatic ring optionally substituted by a methyl group, a $C_{5-19}$ heteroaromatic group having hydrogen on the aromatic ring optionally substituted by an ethyl group, a $C_{5-19}$ heteroaromatic group having hydrogen on the aromatic ring

20   optionally substituted by a $C_{3-6}$ linear, branched or cyclic alkyl group, a $C_{5-19}$ heteroaromatic group having hydrogen on the aromatic ring optionally substituted by a methoxy group, a $C_{5-19}$ heteroaromatic group having hydrogen on the aromatic ring optionally substituted by

25   an ethoxy group, a $C_{5-19}$ heteroaromatic group having hydrogen on the aromatic ring optionally substituted by a $C_{3-6}$ linear, branched or cyclic alkyloxy group, a benzyl

group, a benzyl group having hydrogen on the aromatic

ring optionally substituted by a halogen atom, a benzyl

group having hydrogen on the aromatic ring optionally

substituted by a methyl group, a benzyl group having

hydrogen on the aromatic ring optionally substituted by

an ethyl group, a benzyl group having hydrogen on the

aromatic ring optionally substituted by a $C_{3-6}$ linear,

branched or cyclic alkyl group, a 2-phenylethyl group, or

a $C_{3-10}$ linear, branched or cyclic alkyl group having a

$C_{6-20}$ aromatic group bonded thereto, or by the following

formula (2):



(2)

wherein A and $R^1$ are as defined above.

2. An optically active fluorine-containing compound

represented by the following formula (3) or (4):



(3)



(4)

3. A process for producing an optically active

fluorine-containing compound represented by the above

formula (1) or (2), which comprises asymmetrically

epoxidizing an $\alpha,\alpha,\alpha,$-trifluoromethacrylic acid

derivative represented by the following formula (5):

$$\begin{array}{c} CF_3 \\ \diagup\!\!\!\diagdown \\ \quad\quad A\diagdown R^1 \\ \parallel \\ O \end{array} \quad\quad (5)$$
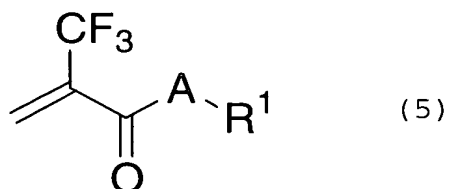
5    wherein A is an oxygen atom, a sulfur atom or an NH group,

and $R^1$ is a methyl group, an ethyl group, a $C_{3-10}$ linear,

branched or cyclic alkyl group, a $C_{6-20}$ aromatic group, a

$C_{6-20}$ aromatic group having hydrogen on the aromatic ring

optionally substituted by a halogen atom, a $C_{6-20}$ aromatic

10   group having hydrogen on the aromatic ring optionally

substituted by a methyl group, a $C_{6-20}$ aromatic group

having hydrogen on the aromatic ring optionally

substituted by an ethyl group, a $C_{6-20}$ aromatic group

having hydrogen on the aromatic ring optionally

15   substituted by a $C_{3-6}$ linear, branched or cyclic alkyl

group, a $C_{6-20}$ aromatic group having hydrogen on the

aromatic ring optionally substituted by a methoxy group,

a $C_{6-20}$ aromatic group having hydrogen on the aromatic

ring optionally substituted by an ethoxy group, a $C_{6-20}$

20   aromatic group having hydrogen on the aromatic ring

optionally substituted by a $C_{3-6}$ linear, branched or

cyclic alkyloxy group, a $C_{5-19}$ heteroaromatic group, a

$C_{5-19}$ heteroaromatic group having hydrogen on the aromatic

ring optionally substituted by a halogen atom, a $C_{5-19}$

heteroaromatic group having hydrogen on the aromatic ring optionally substituted by a methyl group, a $C_{5-19}$ heteroaromatic group having hydrogen on the aromatic ring optionally substituted by an ethyl group, a $C_{5-19}$ heteroaromatic group having hydrogen on the aromatic ring optionally substituted by a $C_{3-6}$ linear, branched or cyclic alkyl group, a $C_{5-19}$ heteroaromatic group having hydrogen on the aromatic ring optionally substituted by a methoxy group, a $C_{5-19}$ heteroaromatic group having hydrogen on the aromatic ring optionally substituted by an ethoxy group, a $C_{5-19}$ heteroaromatic group having hydrogen on the aromatic ring optionally substituted by a $C_{3-6}$ linear, branched or cyclic alkyloxy group, a benzyl group, a benzyl group having hydrogen on the aromatic ring optionally substituted by a halogen atom, a benzyl group having hydrogen on the aromatic ring optionally substituted by a methyl group, a benzyl group having hydrogen on the aromatic ring optionally substituted by an ethyl group, a benzyl group having hydrogen on the aromatic ring optionally substituted by a $C_{3-6}$ linear, branched or cyclic alkyl group, a 2-phenylethyl group, or a $C_{3-10}$ linear, branched or cyclic alkyl group having a $C_{6-20}$ aromatic group bonded thereto.

4. The process for producing an optically active fluorine-containing compound represented by the above formula (1) or (2), wherein the $\alpha,\alpha,\alpha,$-trifluoromethacrylic acid derivative represented by the

formula (5) is subjected to the asymmetric epoxidizing

reaction in the presence of a catalyst comprising (A) a

rare earth metal alkoxide, (B) optically active 1,1'-bi-

2-naphthol, (C) triphenylphosphine oxide and (D) cumene

5    hydroperoxide or tert-butyl hydroperoxide.

    5. An optically active fluorine-containing compound

represented by the following formula (6) or (7):



(6)



(7)
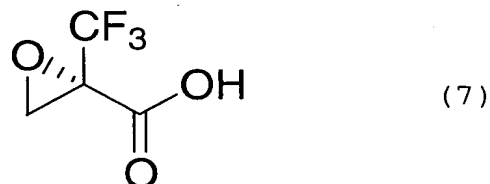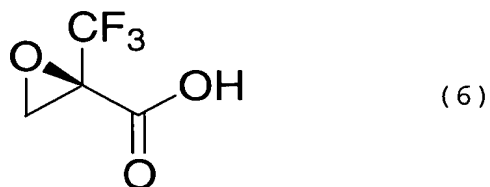
10    6. A process for producing the optically active

fluorine-containing compound represented by the above

formula (6), which comprises hydrolyzing or hydrogenating

the optically active fluorine-containing compound

represented by the above formula (3).

15    7. A process for producing the optically active

fluorine-containing compound represented by the above

formula (7), which comprises hydrolyzing or hydrogenating

an optically active fluorine-containing compound

represented by the above formula (4).

20    8. A process for producing (R)-3,3,3-trifluoro-2-

hydroxy-2-methylpropionic acid, which comprises reacting

the optically active fluorine-containing compound represented by the above formula (6), with a metal hydride.

9. A process for producing (S)-3,3,3-trifluoro-2-hydroxy-2-methylpropionic acid, which comprises reacting the optically active fluorine-containing compound represented by the above formula (7), with a metal hydride.

Now, the present invention will be described in detail.

The optically active fluorine-containing compound represented by the above formula (1) or (2) of the present invention, can be produced by asymmetrically epoxidizing the $\alpha,\alpha,\alpha,$-trifluoromethacrylic acid derivative represented by the above formula (5).

In the present invention, in the above formula (1), (2) or (5), A represents an oxygen atom, a sulfur atom or an NH group. Among them, an oxygen atom is preferred as A.

Further, in the present invention, in the above formula (1), (2) or (5), $R^1$ is a methyl group, an ethyl group, a $C_{3-10}$ linear, branched or cyclic alkyl group, a $C_{6-20}$ aromatic group, a $C_{6-20}$ aromatic group having hydrogen on the aromatic ring optionally substituted by a halogen atom, a $C_{6-20}$ aromatic group having hydrogen on the aromatic ring optionally substituted by a methyl group, a $C_{6-20}$ aromatic group having hydrogen on the

aromatic ring optionally substituted by an ethyl group, a $C_{6-20}$ aromatic group having hydrogen on the aromatic ring optionally substituted by a $C_{3-6}$ linear, branched or cyclic alkyl group, a $C_{6-20}$ aromatic group having hydrogen on the aromatic ring optionally substituted by a methoxy group, a $C_{6-20}$ aromatic group having hydrogen on the aromatic ring optionally substituted by an ethoxy group, a $C_{6-20}$ aromatic group having hydrogen on the aromatic ring optionally substituted by a $C_{3-6}$ linear, branched or cyclic alkyloxy group, a $C_{5-19}$ heteroaromatic group, a $C_{5-19}$ heteroaromatic group having hydrogen on the aromatic ring optionally substituted by a halogen atom, a $C_{5-19}$ heteroaromatic group having hydrogen on the aromatic ring optionally substituted by a methyl group, a $C_{5-19}$ heteroaromatic group having hydrogen on the aromatic ring optionally substituted by an ethyl group, a $C_{5-19}$ heteroaromatic group having hydrogen on the aromatic ring optionally substituted by a $C_{3-6}$ linear, branched or cyclic alkyl group, a $C_{5-19}$ heteroaromatic group having hydrogen on the aromatic ring optionally substituted by a methoxy group, a $C_{5-19}$ heteroaromatic group having hydrogen on the aromatic ring optionally substituted by an ethoxy group, a $C_{5-19}$ heteroaromatic group having hydrogen on the aromatic ring optionally substituted by a $C_{3-6}$ linear, branched or cyclic alkyloxy group, a benzyl group, a benzyl group having hydrogen on the aromatic ring optionally substituted by a halogen atom, a benzyl

group having hydrogen on the aromatic ring optionally

substituted by a methyl group, a benzyl group having

hydrogen on the aromatic ring optionally substituted by

an ethyl group, a benzyl group having hydrogen on the

5   aromatic ring optionally substituted by a $C_{3-6}$ linear,

branched or cyclic alkyl group, a 2-phenylethyl group, or

a $C_{3-10}$ linear, branched or cyclic alkyl group having a

$C_{6-20}$ aromatic group bonded thereto. Among them, $R^1$ is

preferably a tert-butyl group, a phenyl group, a phenyl

10  group having hydrogen on the aromatic ring substituted by

a halogen atom, or a benzyl group, particularly

preferably a benzyl group.

The compound represented by the above formula (1) or

(2) of the present invention is not particularly limited,

15  but specifically, the compound wherein A is an oxygen

atom, and $R^1$ is a $C_{1-10}$ alkyl group may, for example, be

(R)-2,3-epoxy-2-(trifluoromethyl)propionic acid methyl

ester, (R)-2,3-epoxy-2-(trifluoromethyl)propionic acid

ethyl ester, (R)-2,3-epoxy-2-(trifluoromethyl)propionic

20  acid isopropyl ester, (R)-2,3-epoxy-2-

(trifluoromethyl)propionic acid n-butyl ester, (R)-2,3-

epoxy-2-(trifluoromethyl)propionic acid n-butyl ester,

(R)-2,3-epoxy-2-(trifluoromethyl)propionic acid tert-

butyl ester, (R)-2,3-epoxy-2-(trifluoromethyl)propionic

25  acid cyclohexyl ester, (R)-2,3-epoxy-2-

(trifluoromethyl)propionic acid cyclohexylmethyl ester or

(R)-2,3-epoxy-2-(trifluoromethyl)propionic acid 2-

cyclohexylethyl ester.

Further, the compound represented by the above
formula (1) or (2) wherein A is an oxygen atom, and $R^1$ is
a $C_{6-20}$ aromatic group, may, for example, be (R)-2,3-
epoxy-2-(trifluoromethyl)propionic acid phenyl ester,
(R)-2,3-epoxy-2-(trifluoromethyl)propionic acid p-
chlorophenyl ester, (R)-2,3-epoxy-2-
(trifluoromethyl)propionic acid m-chlorophenyl ester,
(R)-2,3-epoxy-2-(trifluoromethyl)propionic acid o-
chlorophenyl ester, (R)-2,3-epoxy-2-
(trifluoromethyl)propionic acid p-bromophenyl ester, (R)-
2,3-epoxy-2-(trifluoromethyl)propionic acid m-bromophenyl
ester, (R)-2,3-epoxy-2-(trifluoromethyl)propionic acid o-
bromophenyl ester, (R)-2,3-epoxy-2-
(trifluoromethyl)propionic acid p-fluorophenyl ester,
(R)-2,3-epoxy-2-(trifluoromethyl)propionic acid m-
fluorophenyl ester, (R)-2,3-epoxy-2-
(trifluoromethyl)propionic acid o-fluorophenyl ester,
(R)-2,3-epoxy-2-(trifluoromethyl)propionic acid p-
methoxyphenyl ester, (R)-2,3-epoxy-2-
(trifluoromethyl)propionic acid m-methoxyphenyl ester or
(R)-2,3-epoxy-2-(trifluoromethyl)propionic acid o-
methoxyphenyl ester.

Further, the compound represented by the above
formula (1) or (2) wherein A is an oxygen atom, and $R^1$ is
a $C_{1-10}$ alkyl group having a $C_{6-20}$ aromatic group bonded
thereto, may, for example, be (R)-2,3-epoxy-2-

(trifluoromethyl)propionic acid benzyl ester, (R)-2,3-epoxy-2-(trifluoromethyl)propionic acid 2-phenylethyl ester, (R)-2,3-epoxy-2-(trifluoromethyl)propionic acid (p-chlorophenyl)methyl ester, (R)-2,3-epoxy-2-(trifluoromethyl)propionic acid (p-bromophenyl)methyl ester or (R)-2,3-epoxy-2-(trifluoromethyl)propionic acid (p-fluorophenyl)methyl ester.

Further, the compound represented by the above formula (1) or (2) wherein A is an NH group and $R^1$ is a $C_{1-10}$ alkyl group, may, for example, be (R)-2,3-epoxy-2-(trifluoromethyl)propionic acid methylamide, (R)-2,3-epoxy-2-(trifluoromethyl)propionic acid ethylamide, (R)-2,3-epoxy-2-(trifluoromethyl)propionic acid isopropylamide, (R)-2,3-epoxy-2-(trifluoromethyl)propionic acid n-butylamide, (R)-2,3-epoxy-2-(trifluoromethyl)propionic acid n-butylamide, (R)-2,3-epoxy-2-(trifluoromethyl)propionic acid tert-butylamide, (R)-2,3-epoxy-2-(trifluoromethyl)propionic acid cyclohexylamide, (R)-2,3-epoxy-2-(trifluoromethyl)propionic acid cyclohexylmethylamide or (R)-2,3-epoxy-2-(trifluoromethyl)propionic acid 2-cyclohexylethylamide.

Further, the compound represented by the above formula (1) or (2) wherein A is an NH group and $R^1$ is a $C_{6-20}$ aromatic group, may, for example, be (R)-2,3-epoxy-2-(trifluoromethyl)propionic acid anilide, (R)-2,3-epoxy-2-(trifluoromethyl)propionic acid p-chlorophenylamide,

(R)-2,3-epoxy-2-(trifluoromethyl)propionic acid m-chlorophenylamide, (R)-2,3-epoxy-2-(trifluoromethyl)propionic acid o-chlorophenylamide, (R)-2,3-epoxy-2-(trifluoromethyl)propionic acid, p-

5     bromophenylamide, (R)-2,3-epoxy-2-(trifluoromethyl)propionic acid m-bromophenylamide, (R)-2,3-epoxy-2-(trifluoromethyl)propionic acid o-bromophenylamide, (R)-2,3-epoxy-2-(trifluoromethyl)propionic acid p-fluorophenylamide, (R)-

10    2,3-epoxy-2-(trifluoromethyl)propionic acid m-fluorophenylamide, (R)-2,3-epoxy-2-(trifluoromethyl)propionic acid o-fluorophenylamide, (R)-2,3-epoxy-2-(trifluoromethyl)propionic acid p-methoxyphenylamide, (R)-2,3-epoxy-2-

15    (trifluoromethyl)propionic acid m-methoxyphenylamide or (R)-2,3-epoxy-2-(trifluoromethyl)propionic acid o-methoxyphenylamide.

        Further, the compound represented by the above formula (1) or (2) wherein A is an NH group, and $R^1$ is a

20    $C_{1-10}$ alkyl group having a $C_{6-20}$ aromatic group bonded thereto, may, for example, be (R)-2,3-epoxy-2-(trifluoromethyl)propionic acid benzylamide, (R)-2,3-epoxy-2-(trifluoromethyl)propionic acid 2-phenylethylamide, (R)-2,3-epoxy-2-

25    (trifluoromethyl)propionic acid (p-chlorophenyl)methylamide, (R)-2,3-epoxy-2-(trifluoromethyl)propionic acid (p-

bromophenyl)methylamide or (R)-2,3-epoxy-2-

(trifluoromethyl)propionic acid (p-

fluorophenyl)methylamide.

The compound represented by the above formula (1) or

(2) of the present invention includes not only the above-

mentioned such (R) isomers, but also (S) isomers which

are antipodes of the (R) isomers. In the present

invention, it is possible to produce the optically active

fluorine-containing compound represented by the above

formula (1) or (2) by asymmetrically epoxidizing an

$\alpha,\alpha,\alpha$-trifluoromethacrylic acid derivative represented by

the above formula (5).

The compound represented by the above formula (5) of

the present invention is not particularly limited, but

specifically, the compound wherein A is an oxygen atom,

and $R^1$ is a $C_{1-10}$ alkyl group, may, for example, be $\alpha,\alpha,\alpha$-

trifluoromethacrylic acid methyl ester, $\alpha,\alpha,\alpha$-

trifluoromethacrylic acid ethyl ester, $\alpha,\alpha,\alpha$-

trifluoromethacrylic acid isopropyl ester, $\alpha,\alpha,\alpha$-

trifluoromethacrylic acid n-butyl ester, $\alpha,\alpha,\alpha$-

trifluoromethacrylic acid n-butyl ester, $\alpha,\alpha,\alpha$-

trifluoromethacrylic acid tert-butyl ester, $\alpha,\alpha,\alpha$-

trifluoromethacrylic acid cyclohexyl ester, $\alpha,\alpha,\alpha$-

trifluoromethacrylic acid cyclohexylmethyl ester or

$\alpha,\alpha,\alpha$-trifluoromethacrylic acid 2-cyclohexylethyl ester.

Further, the compound represented by the above

formula (5) wherein A is an oxygen atom, and $R^1$ is a $C_{6-20}$

aromatic group, may, for example, be $\alpha,\alpha,\alpha$-trifluoromethacrylic acid phenyl ester, $\alpha,\alpha,\alpha$-trifluoromethacrylic acid p-chlorophenyl ester, $\alpha,\alpha,\alpha$-trifluoromethacrylic acid m-chlorophenyl ester, $\alpha,\alpha,\alpha$-

5    trifluoromethacrylic acid o-chlorophenyl ester, $\alpha,\alpha,\alpha$-trifluoromethacrylic acid p-bromophenyl ester, $\alpha,\alpha,\alpha$-trifluoromethacrylic acid m-bromophenyl ester, $\alpha,\alpha,\alpha$-trifluoromethacrylic acid o-bromophenyl ester, $\alpha,\alpha,\alpha$-trifluoromethacrylic acid p-fluorophenyl ester, $\alpha,\alpha,\alpha$-

10   trifluoromethacrylic acid m-fluorophenyl ester, $\alpha,\alpha,\alpha$-trifluoromethacrylic acid o-fluorophenyl ester, $\alpha,\alpha,\alpha$-trifluoromethacrylic acid p-methoxyphenyl ester, $\alpha,\alpha,\alpha$-trifluoromethacrylic acid m-methoxyphenyl ester or $\alpha,\alpha,\alpha$-trifluoromethacrylic acid o-methoxyphenyl ester.

15    Further, the compound represented by the above formula (5) wherein A is an oxygen atom, and $R^1$ is a $C_{1-10}$ alkyl group having a $C_{6-20}$ aromatic group bonded thereto, may, for example, be $\alpha,\alpha,\alpha$-trifluoromethacrylic acid benzyl ester, $\alpha,\alpha,\alpha$-trifluoromethacrylic acid 2-

20   phenylethyl ester, $\alpha,\alpha,\alpha$-trifluoromethacrylic acid (p-chlorophenyl)methyl ester, $\alpha,\alpha,\alpha$-trifluoromethacrylic acid (p-bromophenyl)methyl ester or $\alpha,\alpha,\alpha$-trifluoromethacrylic acid (p-fluorophenyl)methyl ester.

    Further, the compound represented by the above

25   formula (5) wherein A is an NH group, and $R^1$ is a $C_{1-10}$ alkyl group, may, for example, be $\alpha,\alpha,\alpha$-trifluoromethacrylic acid methylamide, $\alpha,\alpha,\alpha$-

trifluoromethacrylic acid ethylamide, $\alpha,\alpha,\alpha$-
trifluoromethacrylic acid isopropylamide, $\alpha,\alpha,\alpha$-
trifluoromethacrylic acid n-butylamide, $\alpha,\alpha,\alpha$-
trifluoromethacrylic acid n-butylamide, $\alpha,\alpha,\alpha$-

5    trifluoromethacrylic acid tert-butylamide, $\alpha,\alpha,\alpha$-
trifluoromethacrylic acid cyclohexyl amide, $\alpha,\alpha,\alpha$-
trifluoromethacrylic acid cyclohexyl methylamide or
$\alpha,\alpha,\alpha$-trifluoromethacrylic acid 2-cyclohexyl ethylamide.

     Further, the compound represented by the above

10    formula (3) wherein A is an NH group, and $R^1$ is a $C_{6-20}$
aromatic group, may, for example, be $\alpha,\alpha,\alpha$-
trifluoromethacrylic acid anilide, $\alpha,\alpha,\alpha$-
trifluoromethacrylic acid p-chlorophenylamide, $\alpha,\alpha,\alpha$-
trifluoromethacrylic acid m-chlorophenylamide, $\alpha,\alpha,\alpha$-

15    trifluoromethacrylic acid o-chlorophenylamide, $\alpha,\alpha,\alpha$-
trifluoromethacrylic acid p-bromophenylamide, $\alpha,\alpha,\alpha$-
trifluoromethacrylic acid m-bromophenylamide, $\alpha,\alpha,\alpha$-
trifluoromethacrylic acid o-bromophenylamide, $\alpha,\alpha,\alpha$-
trifluoromethacrylic acid p-fluorophenylamide, $\alpha,\alpha,\alpha$-

20    trifluoromethacrylic acid m-fluorophenylamide, $\alpha,\alpha,\alpha$-
trifluoromethacrylic acid o-fluorophenylamide, $\alpha,\alpha,\alpha$-
trifluoromethacrylic acid p-methoxyphenylamide, $\alpha,\alpha,\alpha$-
trifluoromethacrylic acid m-methoxyphenylamide or $\alpha,\alpha,\alpha$-
trifluoromethacrylic acid o-methoxyphenylamide.

25    Further, the compound represented by the above
formula (5) wherein A is an NH group, and $R^1$ is a $C_{1-10}$
alkyl group having a $C_{6-20}$ aromatic group bonded thereto,

may, for example, be $\alpha,\alpha,\alpha$-trifluoromethacrylic acid
benzylamide, $\alpha,\alpha,\alpha$-trifluoromethacrylic acid 2-
phenylethylamide, $\alpha,\alpha,\alpha$-trifluoromethacrylic acid (p-
chlorophenyl)methylamide, $\alpha,\alpha,\alpha$-trifluoromethacrylic acid

5    (p-bromophenyl)methylamide or $\alpha,\alpha,\alpha$-trifluoromethacrylic
acid (p-fluorophenyl)methylamide.

In the process of the present invention, a method
for preparing the $\alpha,\alpha,\alpha$-trifluoromethacrylic acid
derivative represented by the above formula (5) is not

10   particularly limited.  However, it may be prepared, for
example, by treating $\alpha,\alpha,\alpha$-trifluoromethacrylic acid with
thionyl chloride to obtain $\alpha,\alpha,\alpha$-trifluoromethacrylic
acid chloride, which is then reacted with an alcohol
represented by R1-A-H, a phenol and an amine in the

15   presence of a base such as triethylamine in a solvent
such as diethyl ether or dichloromethane.

In the process of the present invention, various
asymmetric epoxidizing reactions may be used for the
preparation of the optically active fluorine-containing

20   compound represented by the above formula (1) or (2).
For example, a method of employing titanium
tetraisopropoxide or a tartaric acid derivative, a method
of employing a quaternary ammonium salt such as a
cinchona alkaloid derivative, a method of employing a

25   metal such as zinc, lithium, magnesium or a lanthanoid,
or an asymmetric ligand of e.g. an optically active 1,1'-
bi-2-naphthol derivative, a method of employing an

optically active dioxirane, or a method of employing a
salen-manganese complex, may, for example, be mentioned.
However, in the process of the present invention, it is
preferred to carry out the asymmetric epoxidizing

5   reaction in the presence of a catalyst comprising (A) a
rare earth metal alkoxide, (B) optically active 1,1'-bi-
2-naphthol, (C) triphenylphosphine oxide, and (D) cumene
hydroperoxide or tert-butyl hydroperoxide.

In the process of the present invention, (A) the

10  rare earth metal alkoxide to be used for the asymmetric
epoxidizing reaction, is not particularly limited.
However, specifically, it may, for example, be scandium
trimethoxide, scandium triethoxide, scandium
triisopropoxide, scandium tri-n-propoxide, yttrium

15  trimethoxide, yttrium triethoxide, yttrium
triisopropoxide, yttrium tri-n-propoxide, lanthanum
trimethoxide, lanthanum triethoxide, lanthanum
triisopropoxide, lanthanum tri-n-propoxide, cerium
trimethoxide, cerium triethoxide, cerium triisopropoxide,

20  cerium tri-n-propoxide, praseodymium trimethoxide,
praseodymium triethoxide, praseodymium triisopropoxide,
praseodymium tri-n-propoxide, neodymium trimethoxide,
neodymium triethoxide, neodymium triisopropoxide,
neodymium tri-n-propoxide, samarium trimethoxide,

25  samarium triethoxide, samarium triisopropoxide, samarium
tri-n-propoxide, europium trimethoxide, europium
triethoxide, europium triisopropoxide, europium tri-n-

propoxide, gadolinium trimethoxide, gadolinium

triethoxide, gadolinium triisopropoxide, gadolinium tri-

n-propoxide, terbium trimethoxide, terbium triethoxide,

terbium triisopropoxide, terbium tri-n-propoxide,

5    dysprosium trimethoxide, dysprosium triethoxide,

dysprosium triisopropoxide, dysprosium tri-n-propoxide,

holmium trimethoxide, holmium triethoxide, holmium

triisopropoxide, holmium tri-n-propoxide, erbium

trimethoxide, erbium triethoxide, erbium triisopropoxide,

10    erbium tri-n-propoxide, thulium trimethoxide, thulium

triethoxide, thulium triisopropoxide, thulium tri-n-

propoxide, ytterbium trimethoxide, ytterbium triethoxide,

ytterbium triisopropoxide, ytterbium tri-n-propoxide,

ruthenium trimethoxide, ruthenium triethoxide, ruthenium

15    triisopropoxide or ruthenium tri-n-propoxide.

In the process of the present invention, (A) the

rare earth metal alkoxide is preferably a lanthanoid

triisopropoxide such as lanthanum triisopropoxide, cerium

triisopropoxide, praseodymium triisopropoxide, neodymium

20    triisopropoxide, samarium triisopropoxide, europium

triisopropoxide, gadolinium triisopropoxide, terbium

triisopropoxide, dysprosium triisopropoxide, holmium

triisopropoxide, erbium triisopropoxide, thulium

triisopropoxide, ytterbium triisopropoxide or ruthenium

25    triisopropoxide. Among them, lanthanum triisopropoxide

or ytterbium triisopropoxide is further preferred, and

lanthanum triisopropoxide is particularly preferred.

In the process of the present invention, method of preparing the rare earth metal alkoxide is not particularly limited. Further, with respect to the amount of the rare earth metal alkoxide, it is used usually in an amount of from 0.1 mol% to 30 mol% to the $\alpha,\alpha,\alpha$-trifluoromethacrylic acid benzyl ester to be used in the present invention.

In the process of the present invention, the amount of the optically active 1,1'-bi-2-naphthol to be used for the asymmetric epoxidizing reaction is usually from 1 to 2 times by mol, preferably from 1 to 1.2 times by mol, to the lanthanoid triisopropoxide to be used for the reaction.

In the process of the present invention, the amount of the triphenylphosphine oxide to be used for the asymmetric epoxidizing reaction, is usually from 1 to 5 times by mol, preferably from 1.1 to 3 times by mol, to the lanthanoid triisopropoxide to be used for the reaction.

In the process of the present invention, the amount of cumene hydroperoxide or tert-butyl hydroperoxide to be used for the asymmetric epoxidizing reaction is usually from 1 to 4 times by mol to the lanthanoid triisopropoxide at the time of forming the catalyst, and further, at the time of the reaction, it is used usually in an amount of from 1 to 2 times by mol to the $\alpha,\alpha,\alpha$-trifluoromethacrylic acid benzyl ester to be used for the

reaction.

In the process of the present invention, for the preparation of the optically active fluorine-containing compound represented by the above formula (1), it is

5    particularly preferred to carry out the asymmetric epoxidizing reaction by cumene hydroperoxide by means of a catalyst comprising (A) a lanthanoid triisopropoxide as the rare earth metal alkoxide, (B) (R)-1,1'-bi-2-naphthol as the optically active 1,1'-bi-2-naphthol, (C)

10   triphenylphosphine oxide and (D) cumene hydroperoxide. Likewise, for the preparation of the optically active fluorine-containing compound represented by the above formula (2), it is particularly preferred to carry out the asymmetric epoxidizing reaction by cumene

15   hydroperoxide by means of a catalyst comprising (A) a lanthanoid triisopropoxide as the rare earth metal alkoxide, (B) (S)-1,1'-bi-2-naphthol as the optically active 1,1'-bi-2-naphthol, (C) triphenylphosphine oxide and (D) cumene hydroperoxide.

20   In the process of the present invention, at the time of the asymmetric epoxidizing reaction, a catalyst solution comprising (A) a rare earth metal alkoxide, (B) an optically active 1,1'-bi-2-naphthol, (C) triphenylphosphine oxide and (D) cumene hydroperoxide or

25   tert-butyl hydroperoxide, may preliminarily be prepared, and the substrate and cumene hydroperoxide or tert-butyl hydroperoxide are mixed and supplied to the catalyst

solution, to carry out the reaction. Otherwise, the substrate and cumene hydroperoxide or tert-butyl hydroperoxide may respectively separately supplied to the catalyst solution to carry out the reaction.

5      In the process of the present invention, at the time of the asymmetric epoxidizing reaction, in order to maintain the reaction system to be anhydrous, a zeolite such as powdery or molded molecular sieves 3A or molecular sieves 4A may be used in a proper amount, as
10    the case requires.

In the process of the present invention, the solvent useful for the asymmetrical epoxidizing reaction is not particularly limited. However, specifically, it may, for example, be an ether such as tetrahydrofuran (hereinafter
15    referred to simply as THF), diethyl ether or diisopropyl ether, or an aromatic hydrocarbon such as benzene, toluene or ethylbenzene. Preferred is an ether, and particularly preferred is THF.

In the process of the present invention, with
20    respect to the reaction temperature, the asymmetric epoxidizing reaction can be carried out within a range of from -50°C to 50°C. However, in order to obtain the optically active fluorine-containing compound represented by the above formula (1) or (2) in a high optical purity,
25    it is preferably carried out at a temperature of from -30°C to 10°C.

In the process of the present invention, the

reaction time for the asymmetric epoxidizing reaction varies depending upon the substrate concentration, the amount of the catalyst, the concentration of the catalyst and the reaction temperature and is not particularly

5    limited, but the reaction is usually completed from 2 to 24 hours after adding the substrate.

In the process of the present invention, post-treatment after the asymmetric epoxidizing reaction is not particularly limited. Usually, after decomposing the

10   catalyst by adding a saturated ammonium chloride aqueous solution, excess cumene hydroperoxide is decomposed by e.g. an aqueous sodium hydrogen sulfite solution, followed by purification by e.g. silica gel chromatography, whereby it is possible to obtain the

15   desired optically active fluorine-containing compound represented by the above formula (1) or (2) in an optical purity of from 60 to 95%ee.

The optically active fluorine-containing compound represented by the above formula (6) of the present

20   invention can be produced by hydrolyzing the (2R)-2,3-epoxy-2-(trifluoromethyl)propionic acid derivative represented by the above formula (1). Likewise, the optically active fluorine-containing compound represented by the above formula (7) can be produced by hydrolyzing

25   the (2R)-2,3-epoxy-2-(trifluoromethyl)propionic acid derivative represented by the above formula (2).

The conditions for the hydrolysis of the present

invention are not particularly limited. However, at the
time of hydrolysis of the ester, an alkali metal
hydroxide such as lithium hydroxide, sodium hydroxide or
potassium hydroxide is used in an amount of from 1.2 to 3

5    times by mol to the optically active 2,3-epoxy-2-
(trifluoromethyl)propionic acid derivative to be reacted,
and the reaction is carried out in a mixed solvent of
water and methanol within a temperature range of from 0
to 60°C for from 1 to 12 hours, whereby the compound

10   represented by the formula (6) or (7) can be obtained as
the desired product. Further, with respect to the
hydrolysis of the amide, the reaction is carried out in a
solvent in the presence of from 10 to 100 mol% of
hydrochloric acid within a temperature range of from 0 to

15   60°C for from 1 to 12 hours to obtain the optically
active fluorine-containing compound of the above formula
(6) or (7) as the desired product.

The conditions for post-treatment after the
hydrolysis of the present invention are not particularly

20   limited, and the desired product is obtained by
extraction with a solvent such as ethyl acetate under an
acidic condition.

The optically active fluorine-containing compound
represented by the above formula (6) of the present

25   invention can be produced by hydrogenating (2R)-2,3-
epoxy-2-(trifluoromethyl)propionic acid benzyl ester
represented by the above formula (3) in the presence of a

metal catalyst. Likewise, the optically active fluorine-containing compound represented by the above formula (7) can be produced by hydrogenating the (2S)-2,3-epoxy-2-(trifluoromethyl)propionic acid benzyl ester represented

5 by the above formula (4) in the presence of a metal catalyst. The metal catalyst to be used for the hydrogenation reaction in the processes of the present invention is not particularly limited. However, specifically, platinum, platinum oxide, palladium,

10 palladium hydroxide, rhodium, ruthenium, iridium or Raney nickel may, for example, be mentioned. Further, one having such a metal supported on carbon, alumina, calcium sulfate or the like may be mentioned. Preferred is platinum or platinum oxide.

15 The amount of the metal catalyst to be used for the hydrogenation reaction in the processes of the present invention varies depending upon the type of the catalyst and is not particularly limited. However, it is usually used in an amount of from 0.1 to 20 wt%, as calculated as

20 the metal weight to the optically active 2,3-epoxy-2-(trifluoromethyl)propionic acid benzyl ester represented by the above formula (3) or (4).

The solvent useful for the hydrogenation reaction in the processes of the present invention, is not

25 particularly limited so long as it is inert to the reaction. However, specifically, water, an alcohol such as methanol or ethanol, ethyl acetate, acetic acid, an

ether, benzene, hexane or dioxane may, for example, be mentioned. Among them, preferred is an alcohol, and methanol is particularly preferred.

The reaction temperature and the reaction time for the hydrogenation reaction in the processes of the present invention, vary depending upon the type of the catalyst, but usually the reaction will be completed under atmospheric pressure or an elevated pressure within a range of from $-20°C$ to $30°C$ in from 5 to 24 hours.

In the processes of the present invention, post-treatment after the hydrogenation reaction is not particularly limited. However, usually, after filtering the catalyst off, the solvent is distilled under reduced pressure to obtain the desired optically active fluorine-containing compound represented by the above formula (6) or (7).

In the processes of the present invention, the optically active 2,3-epoxy-2-(trifluoromethyl)propionic acid benzyl ester represented by the above formula (3) or (4), to be used for the hydrogenation reaction, is not necessarily highly pure and, for example, may be used in the form of a composition containing cumyl alcohol as a decomposition product of cumene hydroperoxide, an optically active 1,1'-bi-2-naphthol, triphenylphosphine oxide, etc. After completion of the asymmetric epoxidizing reaction of the $α,α,α$,-trifluoromethacrylic acid benzyl ester, whereby the hydrogenation reaction

will proceed under the above-mentioned reaction
conditions.  In such a case, post-treatment is not
particularly limited, but usually, the catalyst is
filtered off, the solvent is distilled off under reduced
5    pressure, and then ethyl acetate, water and sodium
hydrogen carbonate are added, followed by stirring and
liquid separation, whereupon the aqueous layer is
acidified with e.g. hydrochloric acid and extracted with
ethyl acetate, whereby the desired optically active
10   fluorine-containing compound represented by the above
formula (6) or (7) can be obtained.

By reducing the optically active fluorine-containing
compound represented by the above formula (6) of the
present invention with a metal hydride, it is possible to
15   produce (R)-3,3,3-trifluoro-2-hydroxy-2-methylpropionic
acid.  Likewise, by reducing the optically active
fluorine-containing compound represented by the above
formula (7) with a metal hydride, it is possible to
produce (S)-3,3,3-trifluoro-2-hydroxy-2-methylpropionic
20   acid.

In the processes of the present invention, the metal
hydride to be used for the reduction reaction is not
particularly limited.  However, specifically, sodium
boron hydride, sodium boron trimethoxy hydride, sodium
25   boron cyanide hydride, sodium boron triacetoxy hydride,
lithium boron hydride, lithium boron tri-s-butyl hydride,
lithium boron triethyl hydride, lithium boron tricyamyl

hydride, potassium boron hydride, potassium boron tri-s-butyl hydride, potassium boron tricyamyl hydride, zinc boron hydride, calcium boron hydride, lithium aluminum hydride, lithium aluminum trimethoxy hydride, lithium

5     aluminum tri-t-butoxy hydride, sodium aluminum bis(2-methoxyethoxy) hydride or aluminum diisobutyl hydride, may, for example, be mentioned. Among them, preferred is aluminum diisobutyl hydride.

In the processes of the present invention, the

10    amount of the metal hydride to be used for the reduction reaction is usually from 1 to 5 equivalents to the optically active 2,3-epoxy-2-(trifluoromethyl)propionic acid represented by the above formula (6) or (7).

In the processes of the present invention, the

15    solvent useful for the reduction reaction varies depending upon the type of the metal hydride and is not particularly limited so long as it is inert to the reaction. Specifically, an alcohol such as methanol or ethanol, an ether such as THF, diethyl ether or

20    diisopropyl ether, an aliphatic hydrocarbon such as hexane or heptane, a halogenated hydrocarbon such as dichloromethane or chloroform, or an aromatic hydrocarbon such as benzene or toluene, may, for example, be mentioned. For example, in a case where aluminum

25    diisobutyl hydride is used as the metal hydride, toluene, hexane or the like, or a halogenated hydrocarbon mixture thereof with a dichloromethane or the like, is preferred.

In the processes of the present invention, the reaction temperature and the reaction time in the reduction reaction are not particularly limited, but the reaction will usually be completed within a range of from -100°C to 20°C in from 1 to 24 hours.

In the processes of the present invention, post-treatment after the reduction reaction is not particularly limited, but it is common that methanol is dropwise added at -80°C or lower to terminate the reaction, and the reaction solution is acidified with e.g. hydrochloric acid, and then sodium chloride is added and extracted with ethyl ether to obtain (R)-3,3,3-trifluoro-2-hydroxy-2-methylpropionic acid or (S)-3,3,3-trifluoro-2-hydroxy-2-methylpropionic acid. The obtained optically active 3,3,3-trifluoro-2-hydroxy-2-methylpropinic acid can be recrystallized from a solvent such as toluene to bring the optical purity usually to a level of 99.9%ee or higher.

The present invention provides novel optically active fluorine-containing compounds and thus is industrially useful.

Among the derivatives of the present invention, the optically active 2,3-epoxy-2-(trifluoromethyl)propionic acid benzyl ester represented by the above formula (3) or (4) is capable of easily and efficiently producing optically active 3,3,3-trifluoro-2-hydroxy-2-methylpropionic acid without using an optical resolution

agent or enzyme, and accordingly, the production process of the present invention is a process which is simple and efficient as compared with the conventional processes and which is suitable for mass production, and thus it is industrially very useful.

Now, the present invention will be described in further detail with reference to Examples. However, it should be understood that the present invention is by no means restricted to such specific Examples. The following instruments were used for the analyses of the compounds.

### $^1$H-NMR and $^{13}$C-NMR measurements

Carried out by means of Gemini-200, manufactured by Varian.

### Infrared absorption measurement

Carried out by means of 2000FT-IR, manufactured by Perkin Elmer.

### Elemental analysis

C, H: Carried out by means of 2400IICH, manufactured by Perkin Elmer.

F: Carried out by means of HPLC; column: TSKgel IC-Anion-PWXL PEEK (4.6 mm ID × 750 mm), manufactured by Tosoh Corporation; eluent: 1.3 mM gluconic acid-borax buffer; detector: electrical conductivity tester.

### Mass analysis

Carried out by means of M-80B, manufactured by Hitachi, Ltd.

Measurement of specific rotation

Carried out by means of SEPA-300, manufactured by HORIBA, Ltd.

REFERENCE EXAMPLE 1

Preparation of $\alpha,\alpha,\alpha$-trifluoromethacrylic acid benzyl ester

Into a 500 ml two-necked round-bottomed flask equipped with a condenser and a stirrer, $\alpha,\alpha,\alpha$-trifluoromethacrylic acid (154.0 g, 1.10 mol) and thionyl chloride (170.1 g, 1.43 mol) were charged and refluxed for 5 hours. By distillation, $\alpha,\alpha,\alpha$-trifluoromethacrylic acid chloride (92.6 g) having a boiling point of from 88 to 92°C, was obtained (yield: 53%). Further, as a by-product, $\alpha,\alpha,\alpha$-trifluoromethacrylic acid anhydride (34.0 g) having a boiling point of 106°C/31 mmHg was obtained (yield: 24%).

Into a 1,000 ml three-necked round-bottomed flask equipped with a dropping funnel and a stirrer, benzyl alcohol (54.6 g, 0.51 mol) and diethyl ether (600 ml) were charged, and then, the $\alpha,\alpha,\alpha$-trifluoromethacrylic acid chloride (80.0 g, 0.51 mol) obtained as described above, was dropwise added at -40°C, and then a mixture comprising triethylamine (56.2 g, 0.56 mol) and diethyl ether (100 ml) was dropwise added. The mixture was stirred at -40°C for one hour and then further stirred at 0°C for one hour. To the reaction solution, a saturated ammonium chloride aqueous solution was added, and then,

extracted with diethyl ether and dried over anhydrous

magnesium sulfate, and the solvent was distilled off

under reduced pressure. The residue was purified by

silica gel column chromatography (hexane/ethyl

5    acetate=9/1:vol/vol) to obtain $\alpha,\alpha,\alpha$-trifluoromethacrylic

acid benzyl ester (95.3 g) (yield: 82%).

    <u>Analytical results</u>

    $^1$H-NMR(200 MHz,CDCl$_3$) δ 7.37-7.29(m, 5H), 6.70-

6.67(m, 1H), 6.38-6.37(m, 1H), 5.25(s, 2H).

10   EXAMPLE 1

Preparation of (S)-2,3-epoxy-2-trifluoromethylpropionic

acid benzyl ester

    A 2,000 ml three-necked round-bottomed flask having

a dropping funnel and a stirrer, was flushed with

15   nitrogen, and then, molecular sieves 4A (46.3 g, product

preliminarily dried under reduced pressure at 180°C for 4

hours), (R)-1,1'-bi-2-naphthol (7.29 g, 25.5 mmol),

triphenylphosphine oxide (19.3 g, 69.5 mmol) and THF (250

ml) were added. Stirring was carried out for 5 minutes

20   for dissolution, and then a THF solution (250 ml) of

lanthanum triisopropoxide (7.32 g, 23.2 mmol) was added,

followed by stirring at room temperature for one hour.

Cumene hydroperoxide (7.06 g, 46.4 mmol) was added,

followed by further stirring at room temperature for two

25   hours to prepare a catalyst.

    After confirming that the reaction solution became

green, the reaction solution was cooled to -20°C. Cumene

hydroperoxide (89.8 g, 0.59 mol) was added, and then a
THF (500 ml) solution of $\alpha,\alpha,\alpha$-trifluoromethacrylic acid
benzyl ester (106.6 g, 0.46 mol) was dropwise added over
a period of one hour from the dropping funnel. After
5   stirring at -20°C for 12 hours, disappearance of the raw
material was confirmed by $^1$H-NMR.

A saturated ammonium chloride aqueous solution (300
ml) and a 5% sodium hydrogen sulfite aqueous solution
(200 ml) were added to terminate the reaction, whereupon
10   insoluble matters were filtered off by celite filtration,
followed by liquid separation. The organic layer was
concentrated and then, starting point components were
removed by silica gel column chromatography (hexane/ethyl
acetate=3/1:vol/vol). Further purification was carried
15   out by silica gel column chromatography (hexane/ethyl
acetate=9/1:vol/vol) to obtain (S)-2,3-epoxy-2-
trifluoromethylpropionic acid benzyl ester (104.7 g)
(yield: 92%, optical purity: 78 ee%). Here, the
measurement of the optical purity was carried out under
20   the following conditions.

Column: CHIRALCEL OD-H (4.6 mmID × 250 mm),
manufactured by Daicel.

Eluent: hexane/isopropanol=9/1(vol/vol)

Flow rate: 1.0 ml/min

25   Detector: UV=254 nm

Retention time: 10.3 min (S), 11.2 min(R).

The (S)-2,3-epoxy-2-trifluoromethylpropionic acid

benzyl ester obtained in Example 1 was isolated and purified by means of an optical resolution column (CHIRALCEL OD-H, manufactured by Daicel) and analyzed. The physical property values are shown below.

Analytical results

$^1$H-NMR(200 MHz,CDCl$_3$) δ 7.48-7.26(m, 5H), 5.36-5.22(m, 2H), 3.27-3.19(m, 2H)

$^{13}$C-NMR(50 MHz,CDCl$_3$) δ 163.40, 134.15, 128.74, 128.70, 128.19, 121.45(q, J=276.5 Hz), 68.30, 53.94(q, J=37.6 Hz), 49.02

IR (KBr: γ cm$^{-1}$) 3037, 2965, 1755, 1499, 1457, 1389, 1331, 1237, 1179, 1148, 1078, 1030, 958, 870, 782, 752, 696

Elemental analysis: C53.67, H3.68, F23.42 (Calc.: C53.64, H3.74, F23.15)

MASS (m/z) 246 (M+)

Specific rotation (α)$_D^{25}$=9.8° (C=2.0, methanol)

EXAMPLE 2

Preparation of (R)-2,3-epoxy-2-trifluoromethylpropionic acid benzyl ester

The reaction was carried out in the same manner as in Example 1 by using (S)-1,1'-bi-2-naphthol instead of (R)-1,1'-bi-2-naphthol, to obtain (R)-2,3-epoxy-2-trifluoromethylpropionic acid benzyl ester (yield: 90%, optical purity: 78 ee%). $^1$H and $^{13}$C-NMR and IR spectrum data were the same as shown in Example 1.

Analytical results

Elemental analysis: C53.45, H3.78, F2,3.09 (Calc.: C53.64, H3.74, F23.15)

Specific rotation $(\alpha)_D^{25}=9.8°$ (C=2.0, methanol)

EXAMPLE 3

Preparation of (S)-2,3-epoxy-2-trifluoromethylpropionic acid

Into a 500 ml three-necked round-bottomed flask equipped with a stirrer, (S)-2,3-epoxy-2-trifluoromethylpropionic acid benzyl ester (20.9 g, 84.9 mmol, 99 ee%) was charged, and 180 ml of methanol was added for dissolution. Platinum oxide (1.63 g) was added, and then, the reaction system was substituted by hydrogen. After stirring at room temperature for 4 hours, platinum oxide was filtered off. The solvent was distilled off under reduced pressure, whereupon (S)-2,3-epoxy-2-trifluoromethylpropionic acid (11.9 g) was obtained (yield: 90%).

Analytical results

$^1$H-NMR(CDCl$_3$) δ 9.28(br, 1H), 3.36-3.25(m, 2H)

$^{13}$C-NMR(CDCl$_3$) δ 168.76, 121.25(q, J=275.6 Hz), 53.71(q, J=38.5Hz)

IR (KBr: γ cm$^{-1}$) 3528, 2928, 1744, 1636, 1388, 1318, 1259, 1179, 1090, 961, 875, 758, 684

Elemental analysis: C30.78, H1.94, F36.38 (Calc: C30.59, H1.80, F36.52)

MASS (m/z) 157 ((M+H)+)

Specific rotation $(\alpha)_D^{25}=10.9°$ (C=2.0, methanol)

EXAMPLE 4

Preparation of (R)-2,3-epoxy-2-trifluoromethylpropionic
acid

The reaction was carried out under the same
conditions as in Example 3 by using (R)-2,3-epoxy-2-
trifluoromethylpropionic acid benzyl ester instead of
(S)-2,3-epoxy-2-trifluoromethylpropionic acid benzyl
ester, to obtain (R)-2,3-epoxy-2-trifluoromethylpropionic
acid (yield: 93%). The $^1$H and $^{13}$C-NMR and IR spectrum
data thereof were the same as shown in Example 3.

Analytical results

Elemental analysis: C30.67, H1.72, F36.71 (Calc.:
C30.59, H1.80, F36.52)

Specific rotation $(\alpha)_D^{25}$=-10.9° (C=2.0, methanol)

EXAMPLE 5

Preparation of (S)-3,3,3-trifluoro-2-hydroxy-2-
methylpropionic acid

Into a 500 ml three-necked round-bottomed flask
equipped with a stirrer, a 1.0 M aluminum diisobutyl
hydride/hexane solution (2400 ml, 2.40 mol) was charged
in a nitrogen atmosphere. This solution was cooled
to -80°C. A dichloromethane (600 g) solution of (S)-2,3-
epoxy-2-trifluoromethylpropionic acid (149.82 g, 0.96
mol) was added over a period of two hours from a dropping
funnel. After stirring at -70°C for one hour, stirring
was carried out at -50°C for 6 hours. The reaction
solution was cooled to -80°C, and a mixed solution of

methanol (100 g) and dichloromethane (100 g) was dropwise added over a period of two hours to terminate the reaction. The reaction solution was dropwise added over a period of two hours to 1800 ml of a 18% HCl aqueous

5 solution cooled to 0°C, and then, 160 g of sodium chloride was added. The mixture was extracted twice with 500 ml of diethyl ether, and the solvent was distilled off to obtain (S)-3,3,3-trifluoro-2-hydroxy-2-methylpropionic acid (98.6 g) (yield: 65%). This was

10 recrystallized twice from toluene (400 ml) to obtain (S)-3,3,3-trifluoro-2-hydroxy-2-methylpropionic acid (51.6 g) having an optical purity of 99.9 ee% (yield: 34%). This product shows the same $^{1}$H and $^{13}$C-NMR and IR spectrum data as the already reported (S)-3,3,3-trifluoro-2-hydroxy-2-

15 methylpropionic acid and therefore was determined to be (S)-3,3,3-trifluoro-2-hydroxy-2-methylpropionic acid.

Here, the measurement of the optical purity was carried out as follows. To the obtained crystals, an ether solution of diazomethane was added for

20 methylesterification, and this solution was analyzed by gas chromatography (GC) under the following conditions, whereupon the optical purity was calculated.

Column: CP-Chiracil-Dex CB (0.25 mm × 25 m), manufactured by Chrompak Company.

25 Column temperature: 70°C

Detector: FID

Analytical results

Specific rotation $(\alpha)_D^{25}=-18.9°$ (C=4.0, methanol)

EXAMPLE 6

Preparation of (R)-3,3,3-trifluoro-2-hydroxy-2-methylpropionic acid

5      The reaction was carried out under the same conditions as in Example 5 by using (R)-2,3-epoxy-2-trifluoromethylpropionic acid instead of (S)-2,3-epoxy-2-trifluoromethylpropionic acid, to obtain (R)-3,3,3-trifluoro-2-hydroxy-2-methylpropionic acid (yield: 36%).

10    This product shows the same $^1$H and $^{13}$C-NMR and IR spectrum data as the already reported (R)-3,3,3-trifluoro-2-hydroxy-2-methylpropionic acid and therefore was determined to be (R)-3,3,3-trifluoro-2-hydroxy-2-methylpropionic acid.

15      Analytical results

Specific rotation $(\alpha)_D^{25}=18.9°$ (C=4.0, methanol)

REFERENCE EXAMPLE 2

Preparation of $\alpha,\alpha,\alpha$-trifluoromethacrylic acid phenyl ester

20      In the same manner as in Reference Example 1, $\alpha,\alpha,\alpha$-trifluoromethacrylic acid phenyl ester (10.3 g, 47.7 mmol, yield: 63%) was obtained from $\alpha,\alpha,\alpha$-trifluoromethacrylic acid chloride (10 g, 63.0 mmol), phenol (6.5 g, 69.0 mmol) and triethylamine (7.66 g, 75.7

25  mmol).

Analytical results

$^1$H-NMR (200 MHz, CDCl$_3$) δ 7.42-7.14 (m, 5H), 6.94-

6.92 (m, 1H), 6.61-6.60 (m, 1H)

EXAMPLE 7

Preparation of (S)-2,3-epoxy-2-trifluoromethylpropionic
acid phenyl ester

5    A 500 ml three-necked round-bottomed flask equipped
with a dropping funnel and a stirrer was flushed with
nitrogen, and then, molecular sieves 4A (3.7 g, product
preliminarily dried under reduced pressure at 180°C for 4
hours), (R)-1,1'-bi-2-naphthol (529.8 mg, 1.85 mmol),
10   triphenylphosphine oxide (1.54 g, 5.6 mmol) and THF (90
ml) were added. Stirring was carried out for 5 minutes
for dissolution, and then a THF solution (90 ml) of
lanthanum triisopropoxide (585 mg, 1.85 mmol) was added,
followed by stirring at room temperature for one hour.
15   Cumene peroxide (740 µm, 80% pure product, 3.9 mmol) was
added, followed by further stirring at room temperature
for two hours to prepare a catalyst.

After confirming that the reaction solution became
green, the reaction solution was cooled to -20°C. Cumene
20   hydroperoxide (8.4 g, 80% pure product, 44.1 mmol) was
added, and then, a THF (90 ml) solution of $\alpha,\alpha,\alpha$-
trifluoromethacrylic acid phenyl ester (8.0 g, 37.0 mmol)
was dropwise added over a period of one hour from a
dropping funnel. After stirring at -20°C for 12 hours,
25   disappearance of the raw material was confirmed by [1]H-
NMR.

A saturated ammonium chloride aqueous solution (50

ml) and a 5% sodium hydrogen sulfite aqueous solution (10 ml) were added to terminate the reaction, and then, insoluble matters were filtered off by celite filtration, followed by liquid separation. The organic layer was concentrated, and then starting point components were removed by silica gel column chromatography (hexane/ethyl acetate=3/1:vol/vol). Further purification was carried out by silica gel column chromatography (hexane/ethyl acetate=9/1:vol/vol), to obtain (S)-2,3-epoxy-2-trifluoromethylpropionic acid phenyl ester (7.2 g, 31.0 mmol) (yield: 84%, optical purity: 79 ee%). Here, the measurement of the optical purity was carried out under the following conditions.

Analytical results

$^1$H-NMR(200 MHz, CDCl$_3$) δ 7.46-7.13(m, 5H), 3.46-3.41 (m, 1H), 3.36 (d, 1H, J=6.0 Hz)

$^{13}$C-NMR(500 MHz, CDCl$_3$) δ 162.17, 149.57, 129.35, 125.86, 121.42 (q, J=275.9 Hz), 120.84, 54.13(q, J=37.8 Hz), 49.33

IR (KBr: γ cm$^{-1}$) 3511, 3068, 1774, 1592, 1493, 1458, 1386, 1336, 1235, 1187, 1081, 1064, 1024, 1004, 959, 924, 877, 833, 747, 700, 687

Elemental analysis: C51.56, H3.18, F24.47 (Calc: C51.74, H3.04, F24.55)

MASS (m/z) 232 (M+)

Specific rotation $(α)_D^{25}$=0.9° (C=2.0, methanol)

EXAMPLE 8

Preparation of (S)-2,3-epoxy-2-trifluoromethylpropionic
acid

Into a 100 ml three-necked round-bottomed flask
equipped with a dropping funnel and a stirrer, the (S)-
2,3-epoxy-2-trifluoromethylpropionic acid phenyl ester
(7.2 g, 31.0 mmol) obtained in Example 7, methanol (20
ml) and water (20 ml) were charged and cooled to 0°C on
an ice bath, whereupon 3N sodium hydroxide aqueous
solution (30 ml, 90 mmol) was dropwise added over a
period of one hour by means of the dropping funnel, and
stirring was further carried out at the same temperature
for one hour. After completion of the reaction, methanol
was distilled off, followed by extraction with
diisopropyl ether (30 ml × twice). Then, hydrochloric
acid was added to adjust the pH to 3, followed by
extraction with ethyl acetate (30 ml × 3 times). The
obtained organic layer was dried over anhydrous magnesium
sulfate, followed by filtration and concentration to
obtain the desired (S)-2,3-epoxy-2-
trifluoromethylpropionic acid (4.17 g, 26.7 mmol, yield:
87%, optical purity: 78%ee).

REFERENCE EXAMPLE 3

Preparation of α,α,α-trifluoromethacrylic acid (p-
chloroanilide)

In the same manner as in Reference Example 1, α,α,α-
trifluoromethacrylic acid (m-chloroanilide) (14.5 g, 58.0

mmol, yield: 92%) was obtained from $\alpha,\alpha,\alpha$-trifluoromethacrylic acid chloride (10 g, 63.0 mmol), m-chloroaniline (8.9 g, 69.4 mmol) and triethylamine (7.00 g, 69.4 mmol).

Analytical results

$^1$H-NMR (200 MHz, CDCl$_3$) δ 7.68-7.13 (m, 4H), 6.68-6.65 (m, 1H), 6.38-6.37 (m, 1H)

EXAMPLE 9

Preparation of (S)-2,3-epoxy-2-trifluoromethylpropionic acid (m-chloroanilide)

A 1,000 ml three-necked round-bottomed flask equipped with a dropping funnel and a stirrer was flushed with nitrogen, and then, molecular sieves 4A (3.70 g, product preliminarily dried under reduced pressure at 180°C for 4 hours), (R)-1,1'-bi-2-naphthol (2.11 g, 7.37 mmol), triphenylphosphine oxide (6.15 g, 22.1 mmol) and THF (100 ml) were added. Stirring was carried out for 5 minutes for dissolution, and then, a THF solution (100 ml) of lanthanum triisopropoxide (2.33 g, 7.37 mmol) was added, followed by stirring at room temperature for one hour. Cumene hydroperoxide (2.80 g, 80% pure product, 14.7 mmol) was added, followed by further stirring at room temperature for two hours, to prepare a catalyst.

After confirming that the reaction solution became green, the reaction solution was cooled to -20°C. Cumene hydroperoxide (6.31 g, 80% pure product, 33.16 mol) was added, and then a THF (100 ml) solution of $\alpha,\alpha,\alpha$-

trifluoromethacrylic acid (m-chloroanilide) (9.20 g, 36.8 mmol) was dropwise added over a period of one hour from the dropping funnel. After stirring at -20°C for 12 hours, disappearance of the raw material was confirmed by $^1$H-NMR.

A saturated ammonium chloride aqueous solution (200 ml) and a 5% sodium hydrogen sulfite aqueous solution (150 ml) were added to terminate the reaction, whereupon insoluble matters were filtered off by celite filtration, followed by liquid separation. The organic layer was concentrated and then, starting point components were removed by silica gel column chromatography (hexane/ethyl acetate=3/1:vol/vol). Further purification was carried out by silica gel column chromatography (hexane/ethyl acetate=9/1:vol/vol), to obtain (S)-2,3-epoxy-2-trifluoromethylpropionic acid (m-chloroanilide) (7.54 g, 28.5 mmol) (yield: 77%, optical purity: 84 ee%).

Analytical results

$^1$H-NMR(200 MHz, CDCl$_3$) δ 7.68-7.10(m, 4H), 4.12 (d, 1H, J=4.4Hz), 3.19 (d, 1H, J=4.4 Hz)

Elemental analysis: C54.12, H2.87, N5.19, C113.19, F21.35 (Calc: C45.22, H2.66, N5.27, C113.35, F21.46)

MASS (m/z) 265 (M+)

Specific rotation (α)$_D^{25}$=7.3° (C=2.0, methanol)

EXAMPLE 10

Preparation of (S)-2,3-epoxy-2-trifluoromethylpropionic acid

Into a 300 ml round-bottomed flask equipped with a stirrer, the (S)-2,3-epoxy-2-trifluoromethylpropionic acid (m-chloroanilide) (7.54 g, 28.5 mmol) obtained in Example 9, methanol (100 ml) and 35% hydrochloric acid (25 ml) were charged and stirred at room temperature for 4 days.

After completion of the reaction, methanol was distilled off, followed by extraction with ethyl acetate (30 ml × three times). The obtained organic layers were put together and washed with 1N hydrochloric acid (20 ml × twice), followed by drying over anhydrous magnesium sulfate, filtration and concentration to obtain the desired (S)-2,3-epoxy-2-trifluoromethylpropionic acid (2.75 g, 17.6 mmol, yield: 62%, optical purity: 84%ee).

The entire disclosure of Japanese Patent Application No. 2002-340758 filed on November 25, 2002 including specification, claims and summary is incorporated herein by reference in its entirety.